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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/764,628	TROCHON ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *3* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2 and 4-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 are pending in this application and subject to restriction.

Election/Restrictions

Claim 3 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/8/06.

Claim Objections

Claims 1 and 8-12 are objected to as being drawn to non-elected subject matter.

Claim 5 is objected to because of the following informalities: applicants recite that the nucleic acid is joined to "a vector of expression", which is recommended to be recited as -- an expression vector--. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 2 and 4-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4 and 8-12 are vague and indefinite in that the metes and bounds of the term "derivative" are unclear. It is unclear the nature and number of steps required to obtained a

"derivative" of SEQ ID NO: 1, for example. The term implies a number of different steps that may or may not result in a change in the functional characteristics of the nucleic acid from the source that it is "derived from". Furthermore, it is unclear to what the word "thereof" refers, SEQ ID NO:1, the polynucleotide, disintegrin domain or adamalysin.

Claim 1 is vague and indefinite in that the metes and bounds of "inhibiting angiogenesis or invasion or formation of metastases" are unclear. It is unclear what is to be inhibited, metastases as relates to its formation, invasion and angiogenesis or if each of these processes are independent events that are being inhibited.

Claim 5 is vague and indefinite in that the metes and bounds of "nucleic acid comprises a vector or is joined to a vector of expression" are unclear. It is unclear how the nucleic acid, which is a subcomponent of a vector and comprises a disintegrin domain can "comprise a vector" The vector usually comprises such a coding sequence.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2 and 4-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of administering and expressing the disintegrin domain from SEQ ID NO: 1 Met 420 to Gly 511 of SEQ ID NO: 1 at a site to be targeted for diminution of the number of intratumoral vessels, for inhibition of growth of melanoma and for inhibition of pulmonary metastases, does not reasonably provide enablement for any other

embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Nature of invention. The instant claims are drawn to a methods of inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis.

2) Scope of the invention. The number of disease and conditions to be treated is of extremely broad scope. Each of the claims recite a single step of "administering a therapeutically effective amount of an active" nucleic acid coding for part or all of the disintegrin domain of an adamalysin or a derivative thereof. The specific adamalysin to be used is metargidin, which is disclosed as SEQ ID NO: 1, complements or derivatives thereof. The nucleic acid can code for all or part of either of these molecules. The claims do not limit the part to a specific activity and therefore, the part can be as small as dinucleotides to the entire coding nucleic acid which in the case of SEQ ID NO:1 is 276 nucleotides. Hence, the scope of the nucleic acid to be used is also quite broad in that the number of derivatives of the genus of

adamalysins or SEQ ID NO:1 or parts or complements of either of these sequences is extremely broad.

3) State of the art. The adamalysin family functions in proteolysis, adhesion, fusion and intracellular signaling (see Ruben et al, US 2002/0182702 ¶ 1042). The art teaches that there are two subfamilies of adamalysins 1) snake venom metalloproteases (SVMPs) and 2) the ADAMS (proteins with a disintegrin domain and a metalloprotease domain). Multiple ADAMS have been identified including ADAM1, ADAMTS-1, fertilin (ADAM2), cryitestin (ADAM3), epididymal apical protein I, meltrin, MS2, TNF-a converting enzyme, Kusbanian and metargidin (see Ruben et al, ¶ 0004). Within the ADAMS, the disintegrin domain functions to prevent integrin-mediated cell to cell and cell to matrix interactions such as plated aggregration, adhesion, migration of tumor cells or neutrophils or angiogenesis. There have been multiple propositions that members of the adamalysin family have a potential to treat a myriad of conditions such as those recited here (see Ruben et al US 2002/0165377 and Young et al (US 2003/0194797 in which the role of ADAM-22 and any other ADAM protein in inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis is proposed), but these propositions have not lead to the identification of any treatments that are viable options against diseases.

4) Guidance in the specification. The specification states that metargidin comprises AMEP (anti-angiogenic metargidin peptide) is a human protein with multipotent function including blocking angiogenic functions of integrin alpha v beta, inhibition of migration and formation of capillary structures and functions proapototically independent of modification of

their cell cycle. The disintegrin domain constitutes Met 420 to Gly 511 of SEQ ID NO:1. As to derivatives, the specification teaches (¶ 0039), "The derivatives can be fragments of truncated form, sequences modified by deletion, addition, suppression or replacement of one or more amino acids. The derivatives can also be fragments corresponding to said derivatives constituted by chemically modified amino acids, these modifications making the derivatives more stable. The invention also pertains to polynucleotide sequences coding for said derivatives." Hence the scope of the recite nucleic acid is enormous. Applicants synthesize AMEP in bacteria and demonstrate that this protein can function to inhibit adhesion of fibrinogen to vitronectin and fibronectin, inhibit endothelial cell migration, proliferation, capillary formation and stimulates proapoptosis in endothelial cells *in vitro*. *In vivo,* AMEP nucleic acid was electrotransferred to muscle of nude and C57B1/6 mice and inhibited growth of MDA-MB-231 tumor growth and formation of pulmonary metastases in syngeneic mice.

5) **Unpredictability of the art**. The enablement of the instant invention has been assessed in light of the specification and the prior art available at the time of filing. "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). In the instant case, there are multiple inoperative embodiments when considering the use of the instant invention in humans such as 1) the claims recite broadly use of a nucleic acid or parts or complements or derivatives of any of these with the only requirement that it code for a

disintegrin domain, reciting no functional requirements of the domain and 2) as well applicants recite a broad and diverse range of ailments that are to be treated and conditions that are to be inhibited and 3) the lack of recited route of administration of the nucleic acid exacerbate the unpredictability of the art. In light of the art at the time of filing, the instant invention would require undue experimentation to perform the invention in humans.

The instant invention is unpredictable for inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis in humans for the following reasons. First, applicants' invention is based upon the premise that the disintegrin domain of amadalysin can be used therapeutically to treat a variety of conditions. The claims are directed to a broad and diverse genus of disintegrin parts, complement and derivatives molecules from any adamalysin. However, the specification teaches (¶ 0032), "The physiological role of the different adamalysins is extremely varied: regulation of cell adherence, release of a ligand, activation of a receptor, cell fusion (review, Primakoff and Myles, 2000). However, the mode of action of these molecules remains unknown" (emphasis added). The specification is directed specifically to the analysis of AMEP, the disintegrin domain of metargidin encoded by Met 420 to Gly 511 of SEQ ID NO:1. As well, the invention is practiced using this peptide and the results to do demonstrate any understanding of the mode of action or the general nature of the effects of AMEP, (¶ 0093) "The set of results obtained show that AMEP possesses an antiangiogenic activity that is greater than that of the 1.4-kDa peptide. Given that both AMEP and the 1.4-kDa peptide possess an RGD sequence implicated in bonding endothelial cells to alpha v beta 3 integrins, we believe that the action of AMEP is not limited to blocking the functions of the alpha v beta 3 integrin. AMEP

appears to possess its own activity which could be linked to modifications of the signalization at the cellular level (message that could be transported by the integrin alpha v beta 3 and/or metargidin)." The disclosure does not provide adequate guidance for the use of any part of any derivative of any disintegrin domain from any adamalysin and hence the recited goals are highly unpredictable. Therefore, the efficacy of the instant invention lies in the use Met 420 to Gly 511 of SEQ ID NO:1 and while the structural requirements for this peptide alone have been demonstrated, the specification ahs not demonstrated what amino acids, sequences or regions can be altered to mediate the same activity. As well, the mechanism of action (or actual functional requirements) are unknown which exacerbates the ability to identify those sub regions required to mediate the function that leads to the effects noted in the application..

Secondly, applicants do not demonstrate nor is it known in the art that this peptide can mediate all of the recited functions. The claims recite that the broad genus of disintegrin adamalysin sequences can inhibit angiogenesis, invasion or formation of metastases and yet applicants have only demonstrated that the number of intratumoral vessels can be reduced. Applicants recite that these sequences can treat cancer, inflammatory disease, atherosclerosis, macular degeneration and psoriasis. Of these, applicants have demonstrated that tumor growth alone can be inhibited. Thirdly, the method of delivery of polynucleotides is highly unpredictable to date. Gene delivery has been a persistent problem for gene therapy protocols and the route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Verma et al speak to the problem that is confronted in the art when they teach (Verma and Somia, Nature, September 1997), "The Achilles heel of gene therapy is gene delivery... the problem has been an inability to deliver genes efficiently and to obtain sustained

expression". To present date, no generic mode of gene transfer has provided a viable option for successful gene therapy protocols, which exacerbates the broad and diverse treatments proposed by applicants.

6) **Summary**. The invention recites broadly a method of inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis using a broad genus of molecules. The unpredictability of using the claimed invention for all of these methods is accentuated due to the lack of methods or processes disclosed in the instant specification exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of established protocols and the inability to predict successful administration of the broad genus of molecules: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2 and 4-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Ruben et al (US 2002/0165377; see entire document).

Rubens et al teach treatment of medical conditions using Adam polynucleotides (¶ 0420) such as angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis (see ¶ 0084-0083). According to ¶ 0004, a ADAM protein includes metargidin. While SEQ ID NO:1 is not disclosed, the ADAM molecules are related such that a derivative of SEQ ID NO;1 is encompassed by the molecules disclosed in Rubens et al. Cells are transformed with vectors comprising the genes to express the disintegrin domain (see e.g. ¶ 0179-0183).

Claims 1 and 4-12 are rejected under 35 U.S.C. 102(a) as being anticipated by Young et al (US 2003/0194797; see entire document).

Young et al teach treatment of medical conditions using ADAM 22 polynucleotides (¶ 0492) such as angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis (see ¶ 0417 and 0492). While SEQ ID NO:1 is not disclosed, the ADAM 22 molecule related to SEQ ID NO:1 by its disintegrin domain and as such derivatives of disintegrin are encompassed by the molecules disclosed in Young et al. Cells are transformed with vectors comprising the genes to express the disintegrin domain (see e.g. ¶ 228).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER